REVIEW

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Macrolide therapy of chronic rhinosinusitis*

Anders Cervin[1] and Ben Wallwork[2]

[1] Department of Oto-Rhino-Laryngology, Head and Neck Surgery, Lund University, Sweden
[2] Department of Otorhinolaryngology, Princess Alexandra Hospital and School of Biomolecular and Biomedical Science, Griffith University Brisbane, Australia

SUMMARY

There is growing evidence that several antibiotics exert their beneficial effect not only by inhibiting or killing bacterial pathogens but also by down-regulating pro-inflammatory mechanisms. This review aims to give an overview of the immunomodulatory properties of macrolide antibiotics in chronic rhinosinusitis and to present a treatment algorithm for managing the difficult CRS patient with long-term, low-dose macrolide antibiotics.

The most prominent effect of macrolides noted in vitro is the inhibition of pro-inflammatory cytokines such as interleukin-8. This effect is probably secondary to inhibition of the activation of transcription factor NF-κB. As a result an attenuation of neutrophilic inflammation takes place. Moreover, macrolides inhibit bacterial virulence and biofilm formation. In vivo, a reduction of pro-inflammatory cytokines is evident in nasal lavage as well as a reduction in nasal secretions. The clinical effect is shown in less facial pain, less headache, less post nasal drip, fewer exacerbations of sinusitis and improved quality of life The treatment should be targeted towards the non-atopic patients with bilateral disease whereas in unilateral disease, surgery is the first option. Macrolide resistant bacterial strains have to be monitored, but to date they have not been of clinical importance.

Key words: macrolide, chronic rhinosinusitis, inflammation, erythromycin, clarithromycin, roxithromycin

INTRODUCTION

Macrolides belong to the family of 14 or 15 membered lactone ring antibiotics, originally found in a Philippine soil sample [(1)]. These antibiotics achieve high intracellular concentration and have a spectrum of activity against Gram positive cocci but also intracellular pathogens such as Chlamydia and Mycoplasma. They have been used for decades in treating community acquired airway infections. Recent years have seen an increasing interest in the immuno-modulating actions of antibiotics not only in chronic airway inflammation but also in rheumatology, neurodegenerative disease such as multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease and stroke. This interest in the immuno-modulating effects of antibiotics includes not only macrolides but also tetracyclines, fluoroquinolones and β-lactam antibiotics.

This review is aimed at clinicians and researchers hoping to gain a basic understanding of the effects of macrolides in chronic rhinosinusitis (CRS) and a suggestion for how to manage macrolide treatment in these patients. Data were identified from Pubmed and Cochrane databases as well as reflecting the experience of the authors.

In 1984 Kudoh et al. reported the remarkable improvement of symptoms in erythromycin treated patients suffering from diffuse panbronchiolitis. It was later followed by reports on improved survival rates [(2,3)]. All patients with diffuse panbronchiolitis also suffered from chronic rhinosinusitis and it was observed that the erythromycin therapy was effective in resolving the symptoms from the upper airways as well. Long-term low-dose eythromycin therapy was used primarily in Japan and the first report with an English abstract was published as late as 1991 [(4)]. Since then there has been increasing interest in the role of macrolide antibiotics in the treatment of chronic sinusitis. Of note are the findings that their efficacy is seen at lower doses and with a slower onset compared to the anti-infective effect and in many cases in the absence of an identifiable pathogen. These findings, together with the in vitro research demonstrating the immune-modulating effects of erythromycin and it's derivates has led to the concept of long-term, low-dose macrolide treatment as primarily an immune response modifying treatment and not an anti-bacterial treatment.

An effective host defence mechanism is maintained by a balance of pro-inflammatory and anti-inflammatory pathways within the host immune system. A down-regulation of inflam-

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Table 1. Mechanisms of action of macrolide antibiotics in chronic respiratory disease.

Target	Macrolide action	In vivo/in vitro	Reference
Transcriptionfactors	Suppression of NF-κB and AP-1	In vitro	Wallwork, 2002 Kikuchi, 2002
Cytokine production	Decreased IL-5, IL-8, GM-CSF	In vitro	Wallwork, 2004
	Decreased TGF-β	In vitro	Wallwork, 2002
	Decreased IL-6, IL-8, TNF-α	In vivo	Suzuki, 1997 Gao, 2007 Cigana, 2007
Cytokine production	Increased concentration of anti-inflammatory cytokines IL-1ra, IL-6, IL-10		Tamaoki, 2004
Matrix metalloproteins	Reduction of matrix metalloproteinase-7	In vivo	Yasuda, 2007
Biofilm formation	Altered structure and function of biofilm	In vitro	Wozniak, 2004
Leukocyte adhesion	Reduced expression of cell surface adhesion molecules	In vitro	Linn, 2000
Apoptosis	Accelerate neutrophil apoptosis	In vitro	Inamura, 2000 Aoshiba, 1995
Oxidative burst	Impaired neutrophil oxidative burst	In vitro	Hand, 1990
Mucociliary clearance	Decreased secretions	In vivo	Rubin, 1997
	Improved clearance		Nishi,1995
Bacterial virulence	Inhibited release of elastase, protease, phospholipase C and eotaxin A by *P. aeruginosa*	In vitro	Hirakata, 1992
Viral entry into cell	Inhibit viral entry (protease inhibitor)	In vitro	Kido, 2007

Abbreviations; NF-κB, Nuclear Factor Kappa beta; AP, Activator Protein; IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor; GM-CSF, granulocyt macrophage colony stimulating factor.

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matory response may however negatively affect the host defence mechanisms and jeopardise the host's ability to effectively combat infection. This seems not to be the case with macrolide therapy, instead they are effective biologic response modifiers providing a moderate immune modulating effect against inflammation.

PATHOPHYSIOLOGY OF CHRONIC SINUSITIS

The pathogenesis of CRS is poorly understood but it is likely that CRS is not a single entity but represents many different clinical phenotypes. There are several external factors like bacteria, fungus, virus, and other antigens that may initiate the chronic upper airway inflammation or infection. Furthermore the host response (i.e. patients response) to these different antigens can vary. The same stimuli may give very different results depending on host reactions, which are modified by predisposing conditions, such as asthma, allergy and the innate immune system.

Histopathology in CRS is characterized by hyperplasia of the mucosa, increased number of seromucous glands and a remodelling of the ciliated epithelium to squamous cell epithelium. Furthermore an infiltrate of inflammatory cells are seen such as lymphocytes, plasma cells, eosinophils and neutrophils [5]. It is believed that this leads to a vicious cycle where inflammation initiates mucosal oedema and increased secretion, which in turn leads to blockage of the drainage pathways and stagnation of secretion, which further drives the inflammation.

Pro-inflammatory mediators have been studied extensively in allergic rhinitis and CRS, mostly through biopsies taken from the inferior or middle turbinate. The highly potent chemoattractant for neutrophils, Interleukin-8 (IL-8) has been demonstrated to be found in much higher concentration in CRS than in allergic rhinitis [6]. A large number of other cytokines and chemokines are also increased in CRS as compared to a variety of control tissue. Among those are IL-1, IL-6, IL-8, Tumor Necrosis factor-alpha (TNF-α), IL-3, Granulocyt Macrophage Colony-Stimulating Factor (GM-CSF), Intercellular adhesion molecule-1 (ICAM-1), also called the human rhinovirus receptor or CD54, and transforming growth factor beta (TGF-β) [7, 8]. The interaction between the different inflammatory mediators is complex and data are based mostly on in vitro studies. A hope for the future is to define and classify CRS in different subgroups according to clinical and immunological characteristics (phenotypes). However, for now our understanding of the immune system is limited.

HOW DO MACROLIDES MEDIATE ANTI-INFLAMMATORY EFFECTS?

Mechanisms of action

Macrolides decrease proinflammatory mediators, neutrophil chemotaxis, leukocute adhesion and oxidative burst and increase apoptosis

The inflammatory response is reasonably well described at a cellular level. On stimulation of airway cells by a foreign molecule, such as lipopolysaccharide (a cell wall sugar unique to Gram-negative bacteria), there is production of pro-inflammatory molecules i.e. various cytokines and chemokines. One of those, IL-8 is a potent neutrophil chemoattractant cytokine (signalling to neutrophils to migrate to an area of infection or damage) and has been shown to be one of the principal cytokines involved in chronic sinusitis [7]. IL-8 production by whole sections of chronic rhinosinusitis mucosa in vitro was shown to be reduced in a dose-dependent fashion by clarithromycin. This reduction was equal to that seen when the mucosa was treated with prednisolone [9]. Neutrophils in the nasal discharge of patients with chronic rhinosinusitis secrete approximately twice as much IL-8 as those in peripheral blood, indicating that they are activated and hence may induce further neutrophil migration. Erythromycin at concentrations of 10^{-5} and 10^{-6} has been shown to significantly inhibit IL-8 secretion by exudative neutrophils by 54% and 34% respectively. These drug concentrations are approximately the same as levels found in sinus mucosa and nasal discharge during macrolide therapy [10]. Macrolides therefore seem capable of inhibiting the production of IL-8 by a variety of cell types and may help break the vicious cycle of neutrophil recruitment and further inflammation in chronic airway disease. For an overview see Table 1.

Other cytokines shown to be inhibited by macrolide treatment in vitro include IL-5, GM-CSF and TGF-β [9, 11]. TGF-β was shown to have reduced expression following in vitro treatment of cultured chronic rhinosinusitis mucosa, however, a similar reduction in expression was not seen after 3 months of a low-dose course of macrolide in CRS patients. An example of the important issue of whether the impressive anti-inflammatory effects of macrolides that have been demonstrated in vitro is seen with the in vivo treatment of patients.

Furthermore, anti-inflammatory cytokines such as IL-10 and, depending on the situation, also IL-1 and IL-6 have been shown to be increased in vitro following exposure to macrolides [12].

Nuclear factor-κB (NF-κB) is a key nuclear transcription factor involved in the up-regulation of the inflammatory process. It controls the expression of the genes for multiple cytokines and adhesion molecules [13]. Miyanohara et al. [14] examined the activity of clarithromycin on cultured human nasal epithelial cells and fibroblasts obtained from nasal polyps. They suggested that clarithromycin may decrease the expression of IL-1β mRNA through suppression of activation of NF-κB. Desaki et al. [15] showed that erythromycin inhibited the activation of the transcription factors NF-κB and AP-1 in human bronchial epithelial cells. It is postulated therefore, that macrolides may produce their wide-ranging anti-inflammatory effect by inhibition of the actions of NF-κB.

Macrolides have been shown to accumulate in inflammatory cells at concentrations several hundred-fold higher than concentrations in extracellular fluid. [16]. In addition, inflammatory cytokines have been shown to stimulate the accumulation of macrolides into macrophages [17]. This suggests that at sites of inflammation, cells may accumulate even more macrolide than under normal physiological conditions. This intracellular accumulation may aid macrolides in treating intracellular pathogens, as well as altering host cell intrinsic functions.

Therapeutic induction of apoptosis results in an attenuation of the inflammatory response. Both erythromycin and roxithromycin have been shown to accelerate apoptosis in isolated human neutrophils [18]. Aoshiba et al. [19] reported similar findings with erythromycin, roxithromycin and midecamycin.

Phagocytic cells are capable of producing toxic, reactive oxygen species that are used to destroy phagocytosed micro-organisms. These oxygen species are damaging to bacteria and also potentially to host tissues if generated in excess. Macrolides have been reported to produce a dose-dependent reduction in superoxide production by neutrophils [20, 21].

The adhesion between neutrophils and endothelial cells occurs as an integral part of the inflammatory cascade. Macrolides can reduce inflammatory cell adhesion via inhibition of adhesion molecule expression. This effect may result in reduced recruitment of inflammatory cells at sites of inflammation [22, 23].

Macrolides reduce bacterial adherence, inhibit biofilm formation and decrease bacterial virulence

Macrolides have a well-established antimicrobial activity. They are primarily bacteriostatic and bind to the 50S subunit of the 70S ribosome in prokaryotes, thus inhibiting bacterial protein synthesis. Macrolides are bacteriostatic against Gram-positive cocci (including anaerobes) with the exception of enterococci and have limited Gram-negative activity. At higher concentration macrolides are bacteriocidal. An important feature of macrolide antibiotics is the effect on intra-cellular pathogens such *Corynebacterium diptheriae, Bordetella pertussis, Legionella pneumophila, Mycoplasma pneumoniae* and *Chlamidya pneumoniae* [24]. This is an effect macrolides share with tetracyclines which now also are emerging as immunomodulating.

Some organisms, for example *Pseudomonas aeruginosa*, are resistant to the direct anti-bacterial effect of macrolides. However, macrolides have been shown to attenuate the effect of various virulence factors produced by *Pseudomonas aeruginosa*. It has been shown that erythromycin inhibits the release

of elastase, protease, phospholipase C and eotaxin A [25]. Another study showed that erythromycin was able to suppress the production of toxic lectins, protease and hemolysin, thus reducing the damage to the tissue surrounding the infection [26]. Another example of decreasing the virulence of bacteria is found in a pneumonia mouse model where roxithromycin treatment reduced matrix metalloproteinase-7 expression (metallomattrix proteinase degrades the normal extracellular matrix promoting its replacement with interstitial collagen) and activation and keratinocyte-derived chemokine production in the lungs, while it increased mononuclear cell responses in the lungs, with enhanced bacterial clearance. Concentrations of roxithromycin in plasma and tissues were below the MICs for the inoculated strain during infection. The treatment also reduced inflammatory responses to killed pneumococci in the lungs [27].

Biofilm-producing bacteria such as *Staphylococcus, Haemophilus* and *Pseudomonas* benefit from an enhanced ability stick to a surface, aggregate, communicate, and construct an outer shell, which could be likened to a coral reef.

This biofilm formation leads to a resistance to phagocytosis and a reduction in the efficacy of anti-microbial agents. Macrolides have been shown to alter the structure and function of biofilm produced by *P. aeruginosa* [28, 29]. Azithromycin has been shown to inhibit interbacterial communication (also referred to as quorum-sensing) [30]. Quorum-sensing is important in bacterial virulence factor production and biofilm formation. In conclusion, these findings therefore suggest that macrolides may be able to reduce tissue damage caused by certain bacteria, without exerting a direct antibacterial effect.

Table 2. Clinical studies using macrolides.

Type of study	Dosage 24h (mg)	Duration (months)	Macrolide	Results	Reference
Prospective, double-blind, placebo controlled	150	3	RXM	Improvements in SNOT-20 score, nasal endoscopy, saccharine transit time, and IL-8 levels in lavage fluid ($P < 0.05$)	Wallwork, Cervin et al 2006
Prospective, randomised, n=90	1000 (2 wks) 500 (10 wks)	3	CAM	As effective as surgery in chronic sinusitis	Ragab 2004
Prospective, open, n=17	500	12	EM	12 responders, mucociliary transport, headache, postnasal drip, all improved, $p < 0.05$	Cervin 2002
Prospective, open, n=20	1000	0.5	CAM	Improvement in CD68, IL-6, IL-8, TNF-alpha and clinical parameters	Macleod 2001
Prospective, open, n=20	400	3	CAM	Reduction of IL-8 in nasal lavage, decreased nasal polyp size	Yamada 2000
Prospective, open, n=16	200, 150		CAM, RXM	Patients with normal IgE have higher response rate	Suzuki 2000
Prospective, open, n=20	1000	0,5	CAM	Reduction of secretion volume, improvement in mucociliary transport	Rubin 1997
Prospective, open, n=30	150	3	RXM	Approx. 80% of patients respond. Postnasal drip, headache	Kimura 1997
Prospective, open, n=12	150		RXM	Reduction of nasal IL-8, CT better aeration	Suzuki 1997
Prospective, open? n=45	400	2-3	CAM	Approx. 71% overall improvement	Hashiba 1996
Prospective, open, n=20 (+20 in combination with azelastine)	150	>2	RXM	Reduction of nasal polyps associated with CRS in at least 52% of patients	Ichimura 1996
Prospective, open, n=32	400	1	CAM	Reduction of secretion volume, improvement in mucociliary transport	Nishi 1995
Retrospective, open, n=149	200-600	3-6	EM	Postoperative treatment with EM improves results compared to no treatment, 88% improvement vs. 68%.	Moriyama 1995
Prospective, open, n=16	600	>6	EM	Approx. 85% overall improvement	Iino 1993
Prospective, open	400-600	8	EM	Approx. 60% overall improvement	Kikuchi 1991

EM = Erythromycin, CAM = Clarithromycin, RXM = Roxithromycin.

Macrolides increase mucociliary clearance and reduce mucus hypersecretion

In addition to their anti-inflammatory and antibiotic effects, macrolides produce effects on mucous production and mucociliary clearance. In rabbits, roxithromycin treatment increased the rate of tracheal mucociliary transport [31]. A further animal study demonstrated that goblet cell hypersecretion in the guinea-pig trachea was reduced by clarithromycin [32]. In patients with chronic rhinosinusitis treated with clarithromycin, the abnormal visco-elastic properties of their nasal mucous was improved and thus made more suitable for effective mucociliary clearance [33]. These findings support the observations of clinical studies in which mucous secretion was reduced and mucociliary clearance was increased [34, 35].

Mechanisms of action, a conclusion

Considerable evidence now exists to show that macrolides possess numerous anti-inflammatory and immunomodulatory activities. The most crucial is the inhibition of neutrophilic inflammation through the suppression of IL-8 production, probably secondary to inhibition of NF-κB activation. Moreover, a potentially powerful mechanism is the inhibition of bacterial virulence and biofilm formation. However, it is important to note that in many cases, these in vitro effects are yet to be shown to also be present in vivo.

In the future there is hope for a new group of macrolides without the antibacterial effect, so called "immunolides or designer macrolides" [36]. If they were to be proven effective it would reduce the potential problem of bacterial strains becoming resistant to macrolides and would rule out any doubt that the effects seen from macrolides is truly anti-inflammatory and not secondary to an anti-bacterial effect.

MACROLIDE IMMUNOMODULATION IN CHRONIC RHINOSINUSITIS

Macrolide antibiotics are clinically effective in DPB and asthma

With one recent exception there is a lack of well designed blinded and prospective studies on the effect of long-term, low-dose macrolide therapy in CRS [37]. The majority of clinical trials in CRS have been small and open. The most abundant high quality data currently exists in patients with CF. A short resumé on the clinical effect of macrolides in the lower airways is therefore presented. The remarkable effect on the survival rate in diffuse panbronchiolitis has already been mentioned [2,3]. In Cystic fibrosis (CF) several studies have shown a positive effect, even if the patient is infected with *Pseudomonas aeruginosa*. Effects include a marked reduction of the cytokine levels; TNF-α, IL-8, IL-4 and interferon-gamma and a significant improvement in lung function [38,39]. Other placebo-controlled studies using azithromycin showed an undisputed effect on respiratory and clinical parameters regardless of *Pseudomonal* infection [40-42].

The positive effect in asthma is not as convincing as in CF. But several randomised controlled studies have shown improvement in asthma control, reduced bronchial hyper-responsiveness and reduction in cytokines in sputum [43-45].

In Chronic Obstructive Pulmonary Disease (COPD) the effect is small or lacking [46,47].

In summary, the clinical effect seems to go hand in hand with a reduction of pro-inflammatory cytokines. This suggests an anti-inflammatory effect in vivo. However, not all studies have used a reduced dose of the macrolide and an anti-bacterial effect cannot be entirely ruled out. In one asthma study the effect was most notable where intra-cellular pathogens were present.

Macrolides reduce cytokines and clinical symptoms in CRS

Eleven non-placebo controlled studies have been published on the efficacy of long-term (>2 months) macrolide antibiotics in CRS. Another 3 studies have used macrolides for 1 month or less. Ten of the studies have used a dose lower than the one suggested for an antibacterial effect. Recently the first placebo-controlled study has been published by the present authors confirming results from the open studies [37] (Table 2).

Macrolides reduce inflammatory markers

In a short-term, open study 25 chronic purulent rhinosinusitis patients were treated with clarithromycin 500 mg twice daily for 2 weeks. A significant reduction was seen in eosinophilic activity, macrophages, IL-6, IL-8, TNF-α, and elastase. However, bacterial culture was only performed for Chlamydia pneumonia, which was ruled out. The effect of the treatment lasted only for 2 weeks after cessation of medication [48]. In 2 studies where long-term, (> 2 months), low-dose roxithromycin or clarithromycin was used, a reduction of IL-8 levels in nasal lavage was seen as well as a reduction in the size of nasal polyps [49, 50]. In our placebo controlled trial a reduction of nasal IL-8 was observed in nasal lavage in the treatment group [37]. Taken together with the studies from the lower airways it is clear that low-dose macrolide antibiotics reduce the concentration of cytokines and inflammatory cells in the sinonasal mucosa.

Macrolides facilitates transport of secretions

In a study by Rubin and colleagues in acute rhinosinusitis a 30% increase was found in mucociliary transport after 2 weeks of a relatively high dose of clarithromycin (500 mg twice daily) [51]. Eighteen patients with CRS were treated with clarithromycin 500 mg/d for 4 weeks. The spinability and elasticity was increased and viscosity decreased suggesting secretions that transport and clear more easily [52].

Macrolides shrink polyps

Nasal steroids as the first option in nasal polyposis is well established and should not be abandoned. However, in nasal polyps with signs of chronic infection macrolide treatment may be an adjunctive or alternative therapy. Yamada and co-work-

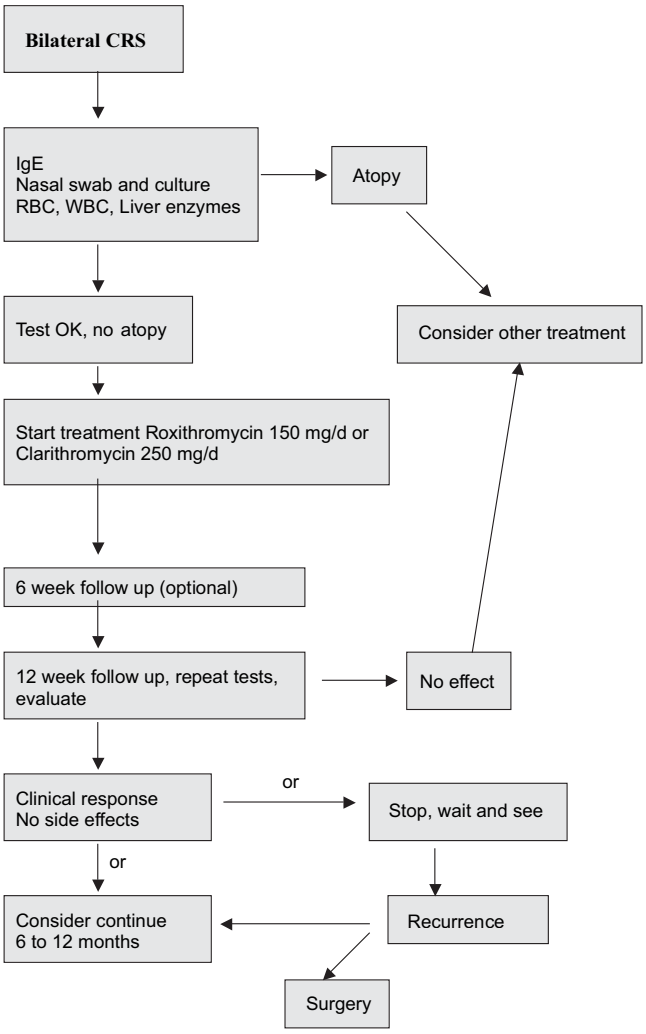

Figure 1. A treatment algorithm for long-term, low-dose macrolide antibiotics in chronic rhinosinusitis. (RBC=Red blood cell count, WBC=White blood cell count).

ers treated 20 patients with CRS and nasal polyps for at least 3 months with clarithromycin 400 mg/d. In the group whose polyps were reduced in size, the IL-8 levels decreased 5-fold. The IL-8 levels were also significantly higher before macrolide treatment than in the group whose polyps showed no change [50]. In another uncontrolled trial 40 patients altogether were treated with either roxithromycin 150 mg alone or in combination with an antihistamine (azelastine) for at least 8 weeks. Smaller polyps were more likely to shrink and this happened in about half of the patients. The investigators found no correlation between treatment effect and the extent of eosinopilia in the tissue [53].

Treat for at least 3 months

Experience from diffuse panbronchiolitis suggests that it takes 6 weeks for the effect of macrolide treatment to set in. And in CRS the rate of improvement is related to the number of weeks the patient is treated. One study showed that response rate varied from 5% at 2 weeks to 71% at 12 weeks [54]. One of our own studies showed that further improvement in responders was seen at 12 months compared to 3 months regarding mucociliary transport, postnasal drip and headache [55].

Macrolides can be used both pre- and post-operatively

Ninety patients with CRS were randomised to either macrolide therapy for 3 months or surgical therapy. Both groups also received a topical steroid and nasal douche with saline. Final assessment was made after 1 year. Both groups showed improvement and there was no significant difference between groups except for nasal volume where surgery was more effective. It was concluded that CRS should be initially targeted with maximal medical therapy before turning to surgery [56]. Unfortunately a placebo group or a group with only topical treatment is lacking.

Persisting CRS after adequate surgery is not uncommon. In one study 57 patients with persisting symptoms of CRS 1 year after sinus surgery were treated with erythromycin in doses initially 600 mg/d reduced approximately every second month by 200 mg. Ninetytwo patients served as controls. The clinical improvement in the treated group was 88% compared to 69% in the untreated patients [57]. An uncontrolled study from our own research group showed that in our most desperate post-surgical cases, 12 out of 17 responded with significant improvement in headache, nasal congestion and postnasal drip as well as improved mucociliary clearance after 3 months of erythromycin 250mg x2. This improvement was further enhanced after 12 months of macrolide therapy [55]. The present data suggests that macrolide therapy works both pre- and post-operatively. For the benefit of the patients and probably from a health economic perspective as well, it is recommendable to try macrolide therapy before surgery, as suggested by the new EPOS2007 document [58].

Prospective randomised controlled trials

As opposed to the lower airways, placebo-controlled trials studying the effects of long-term, low-dose macrolide therapy in CRS have been missing until recently. In a study published by Wallwork et al., 64 patients with CRS and without nasal polyps were recruited. Subjects received either 150 mg roxithromycin daily for 3 months or placebo. Outcome measures included the Sino-nasal Outcome Test-20 (SNOT-20), measurements of peak nasal inspiratory flow, saccharine transit time, olfactory function, nasal endoscopic scoring and nasal lavage assays for IL-8, fucose, and α2-macroglobulin. There were statistically significant improvements in SNOT-20 score, nasal endoscopy, saccharine transit time, and IL-8 levels in lavage fluid ($p < 0.05$) in the macrolide group. A correlation was noted between improved outcome measures and normal IgE levels, whereas patients with elevated IgE were unlikely to respond. No improvement in any outcome was noted in the placebo-treated patients [37]. The result confirms the findings from previous open studies. Additional placebo controlled studies are anticipated in the near future.

MACROLIDES IN THE MANAGEMENT OF CHRONIC RHINOSINUSITIS

How to select patients

From the studies in the lower airways where macrolides are promptly effective in panbronchiolitis and cystic fibrosis, but not so convincing in asthma or COPD it is clear that all airway inflammation is not the same and the phenotype presented by the patients plays an important role. So, are there ways to select patients that are more likely to respond? From the authors own experience, and supported by the Suzuki group, a high level of serum IgE or marked eosinophilia in nasal smear, sinus mucosa or peripheral blood are against a favourable outcome [37,59]. On the other hand, high levels of IL-8 in nasal lavage seems to be positively correlated to a favourable outcome [50]. From other author's experience, macrolide therapy has been found to not be beneficial in primary ciliary dyskinesia (K. Ichimura, personal communication). The patient most likely to respond is the one with persistent purulent discharge where nasopharyngeal culture is negative, no atopy and experiencing little or no effect from nasal steroids. See Figure 1 for a treatment algorithm.

Pre-treatment investigation

Allergy testing is advisable. If the history is long, IgG subclasses to rule out the more common immuno-defiencies is recommended. A nasal swab and culture is advised. It can rule out pathogens not susceptible to macrolide antibiotics. Red and white blood cell counts as well as liver enzymes should be performed although hepatic side effects are rare and reversible. Follow-up with new blood tests and nasal swab after 3 months is advisable. If treating with high doses extending over several years there is the potential of ototoxicity and audiograms at regular intervals is recommended.

Practical management

In choosing a macrolide, erythromycin, roxithromycin and clarithromyciin have all shown effect in open studies in CRS. Erythromycin is the oldest and less expensive, but has more gastrointestinal tract side effects, and is more likely to interact with other drugs. Erythromycin and roxithromycin are both documented to be effective in randomised controlled trials in CRS, [37, 56]. Azithromycin has not been used in CRS, but its efficacy has been proven in the lower airways. Consider the possible interactions between macrolide antibiotics and most importantly dicumarol, anti-epileptic drugs, terphenadine, methrotrexate and anti-depressant drugs.

Low-dose is considered as one half the dose used for treating respiratory infections. On may start with a standard dose for a few weeks and some studies support the view that this will relieve the symptoms quicker than starting with the lower dose [56,57]. However it may increase the risk of side effects.

The patient has to be informed and accept that the effect sets in very slowly. About half of the patients experience improvements after 4 to 6 weeks of therapy. But it may take longer, up to 10 weeks before the patient notices an improvement. A treatment period of 12 weeks before a proper evaluation of the efficacy of the treatment is made. One may want to see the patient in the office or contact by telephone after 6 weeks, to check for side effects and to encourage those patients who have yet to experience improvement.

How long is it advisable to continue? There is no definite answer. In one of our own studies, further improvement was seen in a small group of patients at 12 months compared to 3 months [55]. The strategy in most cases would be to stop treatment after 3 to 6 months and wait and see. Some patients remain improved, but for others recurrence may come as soon as a month after therapy has stopped. Unfortunately data on recurrence rates are missing. If recurrence occurs, it is possible to start again and if the patient responded the first time it is very likely that it will work in the future as well. Another strategy in the difficult patient is to treat during infectious prone months (winter) and take a break during the summer months.

If during treatment, a macrolide resistant bacteria emerges it is our experience that it is best to stop the medication. Repeat nasal culture after a couple of weeks will usually show that the resistant bacteria have disappeared.

It is our experience that with careful selection long-term, low-dose macrolide treatment will be successful in approximately 70 to 80% of the CRS patients.

CONCLUSION

Adding macrolides to our armamentarium for patients with chronic rhinosinusitis has increased our possibilities to help these unfortunate patients. The anti-inflammatory effects of macrolides in vitro are well documented, but the precise mechanism in vivo needs to be further evaluated. The emerging immunolides may clarify the mechanism of action for macrolides. The clinical documentation is improving with one placebo controlled trial and at least one prospective randomised trial, but further randomised trials are wished for. Patient selection is important, as the treatment is more effective in the non-atopic patient. The treatment should be targeted towards patients with bilateral disease whereas in unilateral disease, surgery is the first option. Macrolide resistant bacterial strains have to be monitored especially if the use of macrolides in the difficult CRS patient is spreading. Future research should include biomarkers to predict a favourable outcome, the role of infection in macrolide treatment, the impact of eosinophilic versus neutrophilic inflammation on the efficacy of macrolide treatment and long-term results.

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Anders Cervin
Helsingborg Hospital
25437 Helsingborg
Sweden

Tel: +46-42-406 3194
Mob Tel: +46-702-16-1899
E-mail: anders.cervin@med.lu.se